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(21) International Application Number: PCT/US96/10789 (22) International Filing Date: 25 June 1996 (25.06.96) (30) Priority Data: 08/496,814 29 June 1995 (29.06.95) US (71) Applicant: McNEIL-PPC, INC. [US/US]; 7050 Camp Hill Road, Fort Washington, PA 19034 (US). (72) Inventor: HELZNER, Eileen; 505 Anthony Drive, Plymouth, PA 19462 (US). (74) Agents: CIAMPORCERO, Audley, A. et al.; Johnson and Johnson, One Johnson & Johnson Plaza, New Brunswick, NJ 08933-7003 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: THE COMBINATION OF TOPICAL NASAL ANTIHISTAMINES AND TOPICAL NASAL STEROIDS		
(57) Abstract Nasal spray or nasal drops for the treatment of allergic rhinitis are disclosed comprising: a) an effective amount of a topical antihistamine to relieve histamine mediated symptoms where said topical nasal antihistamine is selected from the group consisting of levocabastine, azelastine and azatadine; b) an effective amount of a topical nasal steroid to reduce inflammation where said nasal steroid is selected from the group consisting of beclomethasone, flunisolide, triamcinolone, dexamethasone and budesonide; and c) sterile water.		

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THE COMBINATION OF TOPICAL NASAL ANTIHISTAMINES AND TOPICAL NASAL STEROIDS

The present invention relates to prevention and treatment of the symptoms of seasonal and perennial allergic rhinitis. More particularly, the present invention relates to the prevention and treatment of the symptoms of seasonal and perennial allergic rhinitis by the application of a combination of topical nasal antihistamines and topical nasal steroids.

BACKGROUND OF THE INVENTION

Seasonal allergic rhinitis is most frequently caused by pollen, pollen fragments and mold spores. The airborne pollens, pollen fragments and mold spores are deposited on the nasal mucosa. In sensitive individuals, rhinitis symptoms develop which include puffy, sore eyes, sneezing, nasal congestion, sinus headaches and fatigue.

The chronic symptoms of perennial allergic rhinitis are most frequently caused by reaction to perennial allergens, such as, house dust mite, mold, cockroach, animal saliva, urine, and dander. The symptoms resemble those of seasonal allergic rhinitis but the duration is year round or episodic depending upon the source of the allergens.

Antihistamines are the primary medicaments employed to treat allergic rhinitis. Antihistamines are helpful to control sneezing, itching, and rhinorrhea as well as associated ocular symptoms but are ineffective in relieving nasal blockage. Antihistamines compete with histamine for binding to H₁ receptors and thereby prevent the action of histamine which includes bronchospasm, edema, increased mucus secretion and itching.

The antihistamines primarily in use today are orally active and administered. However, intranasally (topically) administered antihistamines, including azelastine and levocabastine have also been shown to be useful antihistamines in the treatment of allergic rhinitis. The intranasally administered antihistamines have a quick onset of action because they are delivered directly to the site of activity.

Also employed to treat allergic rhinitis are nasal steroids, particularly the corticosteroids. Such steroids have powerful effects on immunologic and hormonal processes and are very effective in treating the inflammation which accompanies the allergic reaction. Suitable nasal steroids known in use
5 today include beclomethasone, flunisolide, triamcinolone, dexamethasone and budesonide.

SUMMARY OF THE INVENTION

There is provided by the present invention a nasal spray or nasal drops for the treatment of allergic rhinitis comprising:

- 10 a) an effective amount of a topical antihistamine to relieve histamine mediated symptoms where said topical nasal antihistamine is selected from the group consisting of levocabastine, azelastine and azatadine;
- b) an effective amount of a topical nasal steroid to reduce inflammation where said nasal steroid is selected from the group consisting of
15 beclomethasone, flunisolide, triamcinolone, dexamethasone and budesonide; and
- c) sterile water.

DETAILED DESCRIPTION OF THE INVENTION

- 20 The topical antihistamines herein are potent H¹ receptor antagonists which relieve the histamine mediated symptoms, i.e. sneezing, runny nose, itchy nose, etc. The H¹ receptor antagonists block the receptor sites and thereby block the expression of the histamine effect. Thus, persons skilled in the art understand that only a sufficient amount of the antihistamine should be
25 administered to relieve histamine mediated symptoms and no more. This amount will vary depending on whether levocabastine, azelastine or azatadine is employed. In the case of levocabastine from about 0.05 to about 10 mg and preferably from about 0.5 to about 5 mg should be administered in this combination every 4 to 12 hours. In the case of azelastine from about
30 0.05 to about 10 mg and preferably from about 0.5 to about 5 mg should be administered in this combination every 4 to 12 hours. In the case of azatadine, from about 0.05 to about 10 and preferably from about 0.5 to about

5 mg should be administered in this combination every 4 to 12 hours. To achieve these dosage ranges, levocabastine should constitute of the nasal spray or nasal drops composition from about 0.2 to about 40 mg/ml and preferably from about 2 to about 20 mg/ml. To achieve these dosage ranges, azelastine should constitute of the nasal spray or nasal drops composition from about 0.2 to about 40 mg/ml and preferably from about 2 to about 20 mg/ml. Similarly, azatadine should constitute from about 0.2 to about 40 mg/ml and preferably from about 2 to about 20 mg/ml.

10 Levocabastine as used herein includes levocabastine and its pharmaceutically acceptable acid addition salts. Suitable salts include the hydrochloric, hydrobromic, sulfuric, nitric, acetic, propionic, butanedioic, etc. salts. The preferred salt is hydrochloric. Levocabastine, (-)-[3S-1(cis),3,4]-[4-cyano-4-(4-fluorophenyl)cyclohexyl]-3-methyl-4-phenyl-4-piperidine
15 carboxylic acid, is a well known compound and may be prepared by the method of U.S. Pat. 4,369,184, EP 34,415 or Stokbroekx, R. A., et al., *Drug Dev. Res.* 8: 87-93 (1986).

20 Azelastine as used herein, includes azelastine and its pharmaceutically acceptable salts. Preferred are the acid addition salts, such as, the hydrohalo salts and salts with organic acids. Preferred salts include hydrochloridic hydrobromidic, embonic acid, maleic acid, citric acid and tartaric acid salts. Azelastine, 4-(p-chlorobenzyl)-2-[N-methyl-perhydroazepin-4-yl]-1-(2H)-phthalazinone, is a well known compound and may be prepared according to
25 Belg. Pat. 778,269; Vogelsang et al., U.S. Pat. 3,813,384 and Scheffler et al., *Arch. Pharm.* 321, 205 (1988).

Azatadine as used herein includes azatadine and its pharmaceutically acceptable salts. Preferred salts of azatadine include its maleate, sulfate, succinate and acetate salts. Azatadine, 4-aza-5-(N-methyl-4-piperidinyldene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene, is a well known compound and may be prepared according to Belg. Pat. 647,043; U.S. Pat. 3,357,986 and Villani et al., *J. Med. Chem.* 15, 750 (1972).

35 The topical nasal steroids for use herein are corticosteroids which inhibit the release of mediators for the symptoms associated with allergic rhinitis from mast cells and basophils. They also reduce inflammation and

suppress neutrophil chemotaxis. The topical nasal steroids herein have relatively few side effects but are known to cause nasal irritation, drying and epistaxis with use of nasal sprays. Thus, persons skilled in the art understand that only a sufficient amount of nasal steroid should be administered to inhibit mast cell mediator release and inflammation and no more. This amount will vary depending on whether beclomethasone, flunisolide, triamcinolone, dexamethasone or budesonide is employed. Further, the nasal steroids are relatively long acting and alone can be administered once or twice daily. However, when used in conjunction with an active ingredient requiring more frequent administration, the amount of nasal steroid must be adjusted accordingly. For beclomethasone, from about 10 to about 100 mcg, and preferably from about 15 to about 85 mcg should be administered in this combination every 4 to 12 hours. To achieve these dosage ranges, the beclomethasone should constitute of the nasal spray or nasal drops composition from about 0.05 to about 0.5 mg/ml, and preferably from about 0.1 to about 0.3 mg/ml. For flunisolide, from about 30 to about 300 mcg, and preferably from about 50 to about 200 mcg should be administered in this combination every 4 to 12 hours. To achieve these dosage ranges, the flunisolide should constitute of the nasal spray or nasal drops composition from about 0.1 to about 1.0 mg/ml, and preferably from about 0.15 to about 0.5 mg/ml. For triamcinolone, from about 10 to about 100 mcg, and preferably from about 15 to about 85 mcg should be administered in this combination every 4 to 12 hours. To achieve these dosage ranges, the triamcinolone should constitute of the nasal spray or nasal drops composition from about 0.05 to about 0.5 mg/ml, and preferably from about 0.1 to about 0.3 mg/ml. For dexamethasone, from about 40 to about 400 mcg, and preferably from about 60 to about 340 mcg should be administered in this combination every 4 to 12 hours. To achieve these dosage ranges, the dexamethasone should constitute of the nasal spray or nasal drops composition from about 0.2 to about 2.0 mg/ml, and preferably from about 0.4 to about 1.2 mg/ml. For budesonide, from about 40 to about 400 mcg, and preferably from about 60 to about 340 mcg should be administered in this combination every 4 to 12 hours. To achieve these dosage ranges, the budesonide should constitute of the nasal spray or nasal drops composition from about 0.2 to about 2.0 mg/ml, and preferably from about 0.4 to about 1.2 mg/ml.

The corticosteroid topical nasal steroids are, as a general matter, poorly soluble in water. Thus, they are administered in particulate form, as a micronized suspension in a suitable carrier/solvent system. For the treatment of the lung, it is desirable to produce aerosol particle sizes of less than 3 microns. However, in the instant case where it is desirable to treat nasal symptoms, the necessity of producing an aerosol of small particles is removed. For the present invention, it is only necessary to create a stable suspension of the corticosteroid in water which can be delivered by drops or spray directly into the nasal passages. The particle size of the corticosteroid in suspension is not critical so long as the particle is small enough that the amount of compound available for therapeutic activity is not surface area limited and the particle is stable in suspension. The suspension may be maintained with suitable liposomes. Preferably, however, the suspension is maintained by use of solubilizing agents and a suitable surfactant.

Solubilizing agents herein include 1,2-propane diol, 1,3-propane diol, polyethylene glycol having a molecular weight of 100 to 800, dipropylene glycol, or ethanol. A suitable surfactant may be a pharmaceutically acceptable non-ionic, anionic or cationic surfactant. Examples of suitable non-ionic surfactants include glycerol fatty acid esters such as glycerol monostearate, glycol fatty acid esters such as propylene glycol monostearate, polyhydric alcohol fatty acid esters such as polyethylene glycol (400) monooleate, polyoxyethylene fatty acid esters such as polyoxyethylene (40) stearate, polyoxyethylene fatty alcohol ethers such as polyoxyethylene (20) stearyl ether, polyoxyethylene sorbitan fatty acid esters such as polyoxyethylene sorbitan monostearate or polysorbate 20, fatty acid ethanolamides and their derivatives such as the diethanolamide of stearic acid, and the like. Examples of suitable anionic surfactants are soaps including alkali soaps, such as sodium, potassium and ammonium salts of aliphatic carboxylic acids, usually a fatty acids, such as sodium stearate.

Organic amine soaps, also included, include organic amine salts of aliphatic carboxylic acids, usually fatty acids, such as triethanolamine stearate. Another class of suitable soaps is the metallic soaps, salts of polyvalent metals and aliphatic carboxylic acids, usually fatty acids, such as aluminum stearate. Examples of suitable cationic surfactants include amine salts such as octadecyl ammonium chloride, quarternary ammonium compounds such as benzalkonium chloride. Other examples of these and other suitable surfactants can be found in "Pharmaceutical Emulsions and Emulsifying Agents" by Lawrence M. Spatton, second edition; The Chemist and Druggist,

London; "Emulsions' Theory and Practice" by Paul Becher, Reinhold Publishing Corporation, New York; and "Detergents and Emulsifiers, 1969 Annual" by John M. McCutcheon, Morristown, N.J., the disclosures thereof being incorporated herein by reference.

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Only sufficient solubilizing agent and surfactant should be employed to stabilize the suspension/emulsion. Generally there should be employed from about 5 to about 30% w/v and preferably from 10 to about 25% w/v of cosolvent. Likewise, there should be employed from about 0.1 to about 10% w/v and preferably from about 0.5 to about 5% w/v of surfactant.

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Beclamethasone as used herein includes beclamethasone, beclamethasone acetate, beclamethasone valerate, beclamethasone propionate, beclamethasone dipropionate and the like, including the hydrates thereof. Beclamethasone, 9-chloro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione, may be obtained commercially and is prepared according to Brit. Pat. 912,378 and Brit. Pat. 901,093. Beclamethasone is commercially available.

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Flunisolide as used herein includes flunisolide and flunisolide acetate and hydrates thereof. Flunisolide, 6-fluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis(oxy)]pregna-1,4-diene-3,20-dione, may be prepared using *S. roseochromogenes* as in Brit. Pat. 933,867 and Chem. Abst. 60, 3070f (1964) or using *Cunninghamella blakesleeana* as in U.S. pat. 3,124,571. Flunisolide is also prepared in 4,273,710. Flunisolide is commercially available.

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Triamcinolone as used herein includes triamcinolone and its 16- α , 21-diacetate; triamcinolone acetonide, and its 21-acetate, 21-disodium phosphate, and 21-hemisuccinate; triamcinolone benetonide and triamcinolone hexacetonide, including hydrates thereof. Triamcinolone, 9-fluoro-11,16,17,21-tetrahydroxypregna-1,4-diene-3,20-dione, may be prepared according to Bernstein et al., *J. Am. Chem. Soc.* 78, 5693 (1956) and 81, 1689 (1959); Thoma et al., *J. Am. Chem. Soc.* 79, 4818 (1957); U.S. Pat. 2,789,118 or U.S. Pat. 3,021,347. Triamcinolone acetonide may be prepared by stirring a suspension of triamcinolone in acetone in the presence of a trace of perchloric acid. Triamcinolone benetonide may be prepared according to Ger. Pat. 2,047,218 or U.S. Pat. 3,749,712. Triamcinolone

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hexacetonide may be prepared according to U.S. pat. 3,457,348. The triamcinolone and derivatives as taught herein have been sold or are available commercially.

- 5 Dexamethasone as used herein includes dexamethasone and its 21-phosphate, 21-acetate, 21-phosphate disodium salt, 21-dimethylaminoacetate, 21-isonicotinate, 17,21-dipropionate and 21-palmitate. Dexamethasone, (11 β , 16 α)-9-fluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione, may be prepared according to Arth et al., *J. Am. Chem.*
10 *Soc.* 80, 3161 (1958); Oliveto et al., *J. Am. Chem. Soc.* 80, 4431 (1958); U.S. Pat. 3,007,923; Ger. Pat. 1,113,690 or Brit. Pat. 869,511. Dexamethasone is commercially available.

- Budesonide as used herein includes budesonide and its
15 pharmaceutically acceptable salts. Preferred salts of budesonide include its palmitate, laurate, myristate, stearate, oleate, valerate and acetate salts. Budesonide, 16,17-butyldenebis(oxy)-11,21-dihydroxypregna-1,4-diene-3,20-dione, is a well known compound and may be prepared according to U.S. Pat. No. 3,929,768, GB Pat. No. 1,429,922, or A. Thalen, R. L. Brattsand,
20 *Arzneimittel Forsch.* 29, 1787 (1979).

- The nasal spray or nasal drop formulation herein can contain, in addition to the compounds discussed above antimicrobial agents, antioxidants, agents to increase viscosity, isotonic agents, buffers, solubilizing
25 agents, surface active agents and the like. Suitable antimicrobial agents include chlorobutanol, phenylmercuric nitrate, phenyl ethyl alcohol, thimerosal, the quaternary ammonium germicides, such as, benzalkonium chloride, benzethonium chloride or cetylpyridium chloride. Suitable antioxidants include sodium sulfite, sodium ascorbate, oxime sulfate, etc. The
30 preferred isotonic agent is sodium chloride however, other isotonic agents such as dextrose, boric acid and sodium tartrate may be employed. The object of the buffer is to adjust the pH to one compatible with nasal mucous membranes and to stabilize the active ingredient. Ideally the target pH should vary between about 4 and about 6.5. Suitable buffers included phthalate
35 buffers, borate buffers, phosphate buffers, such as $\text{HPO}_4^{2-}/\text{H}_2\text{PO}_4^-$, acetate buffers, such as acetic acid/sodium acetate, a bicarbonate buffer such as $\text{CO}_2/\text{HCO}_3^-$, or a citrate buffer, such as citric acid/citrate, also it may be

adjusted by simply adding an acid such as HCl to achieve the desired acidity. Suitable agents to increase viscosity include polyvinyl alcohol, cellulose derivatives, polyvinylpyrrolidone, polysorbates or glycerine. Suitable surface active agents improve absorption by the nasal mucosa and include polyoxyl 40 stearate, polyoxyethylene 50 stearate, polysorbate 80 and octoxynol.

In general, the concentration of the additives will be in the range as follows:

10	<u>Additive</u>	<u>% W/V</u>
	antimicrobial agent	0.001 - 2.0
	antioxidant	0.01 - 0.20
	isotonic agent	0.01 - 0.50
15	solubilizing agents	0.01 - 1.0
	viscosity builders	0.1 - 2.0
	surface active agents	0.01 - 1.0

The buffer should be added in sufficient amount to achieve the pH range stated above of about 4.0 to about 6.5.

Aerosol formulations and nose drops are prepared as per known techniques. The water employed should be of an appropriate pharmaceutical grade of purified water. These formulations should be administered by drop or spray every 4 to 6 hours to obtain the desired relief.

WHAT IS CLAIMED IS:

1. A nasal spray or nasal drops formulation comprising:
 - a) an effective amount of a topical antihistamine to relieve histamine mediated symptoms where said topical nasal antihistamine is selected from the group consisting of levocabastine, azelastine and azatadine;
 - b) an effective amount of a topical nasal steroid to reduce inflammation where said nasal steroid is selected from the group consisting of beclomethasone, flunisolide, triamcinolone, dexamethasone and budesonide; and
 - c) sterile water.
2. The formulation of claim 1 wherein said topical nasal antihistamine is levocabastine and said topical nasal steroid is selected from the group consisting of beclomethasone, flunisolide, triamcinolone, dexamethasone and budesonide.
3. The formulation of claim 1 wherein said topical nasal antihistamine is azelastine and said topical nasal steroid is selected from the group consisting of beclomethasone, flunisolide, triamcinolone, dexamethasone and budesonide.
4. The formulation of claim 1 wherein said topical nasal antihistamine is azatadine and said topical nasal steroid is selected from the group consisting of beclomethasone, flunisolide, triamcinolone, dexamethasone and budesonide.
5. The formulation of claim 1 wherein said levocabastine constitutes of the nasal spray or nasal drops composition from about 0.2 to about 40 mg/ml; said azelastine constitutes of the nasal spray or nasal drops composition from about 0.2 to about 40 mg/ml; and said azatadine constitutes of the nasal spray or nasal drops composition from about 0.2 to about 40 mg/ml.
6. The formulation of claim 1 wherein said beclomethasone constitutes of the nasal spray or nasal drops composition from about 0.05 to about 0.5

mg/ml; said flunisolide constitutes of the nasal spray or nasal drops composition from about 0.1 to about 1.0 mg/ml; said triamcinolone constitutes of the nasal spray or nasal drops composition from about 0.05 to about 0.5 mg/ml; said dexamethasone constitutes of the nasal spray or nasal drops composition from about 0.2 to about 2.0 mg/ml; and said budesonide constitutes of the nasal spray or nasal drops composition from about 0.2 to about 2.0 mg/ml.

INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/435 A61K31/55 A61K31/445 A61K31/57 //(A61K31/57,
31:435,31:445,31:55)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DRUGS, vol. 45, no. 4, 1993, pages 518-527, XP000603981 HORAK F.: "SEASONAL ALLERGIC RHINITIS" see abstract see page 521, left-hand column, line 8 - page 522, left-hand column, line 41 see page 526, right-hand column, line 1 - line 15</p> <p style="text-align: center;">--- -/--</p>	1-6

☒ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>CLINICAL PHARMACY, vol. 8, no. 7, July 1989, pages 474-485, XP000603999 DELA FUENTE J.C., ET AL.: "PHARMACOTHERAPY OF ALLERGIC RHINITIS" see abstract see page 477; table 1 see page 479, left-hand column, line 13 - page 481, left-hand column, line 35 see page 482, left-hand column, paragraph 3 see page 483, left-hand column, paragraph 2 - paragraph 3</p> <p>---</p>	1-6
Y	<p>J. ALLERGY CLIN. IMMUNOL., vol. 82, no. 5, November 1988, pages 890-900, XP000603998 BUSSE W.: "NEW DIRECTIONS AND DIMENSIONS IN THE TREATMENT OF ALLERGIC RHINITIS" see page 890, left-hand column, paragraph 1 see page 892; table II see page 891, right-hand column, paragraph 4 - page 897, right-hand column, paragraph 2 see page 898, right-hand column, paragraph 1 see page 899, left-hand column, paragraph 2</p> <p>---</p>	1-6
Y	<p>CLINICAL IMMUNOTHERAPEUTICS, vol. 4, no. 4, April 1995, pages 270-278, XP000604030 LUND V.: "PRACTICAL APPLICATION OF THE INTERNATIONAL CONSENSUS ON THE MANAGEMENT OF RHINITIS" see abstract see page 273, left-hand column, paragraph 2 - page 274, right-hand column, paragraph 3 see page 277; table V</p> <p>---</p>	1-6
P,Y	<p>INTERNISTA, vol. 3, September 1995, pages 167-170, XP000604083 PURELLO D'AMBROSIO F., ET AL.: "LEVOCABASTINA VERSUS FLUNISOLIDE NEL TRATTAMENTO DELLA RINITE ALLERGICA PERENNE" see abstract see page 168, left-hand column, line 5 - line 39 see page 168, right-hand column, last paragraph - page 169, left-hand column, line 6</p> <p>---</p> <p>--- -/--</p>	1-6

INTERNATIONAL SEARCH REPORT

Inter. Application No
PCT/US 96/10789

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	HOSPITAL PRACTICE, vol. 31, no. 6, 15 June 1996, pages 61-73, XP000604174 HOLLINGSWORTH: "ALLERGIC RHINOCONJUNCTIVITIS: CURRENT THERAPY" see page 67, middle column, paragraph 2 - page 71, middle column, paragraph 3 see page 67; table 4 ---	1-6
P,Y	ACTA OTORHINOLARYNGOL. , vol. 50, no. 1, January 1996, pages 25-32, XP000604028 WANG D., ET AL.: "THE ACTIVITY OF RECENT ANTI-ALLERGIC DRUGS IN THE TREATMENT OF SEASONAL ALLERGIC RHINITIS" see abstract see page 25, right-hand column, line 1 - line 4 see page 26, right-hand column, line 3 - line 13 see page 28, left-hand column, paragraph 2 - paragraph 4 see page 28, right-hand column, paragraph 3 - page 29, left-hand column, paragraph 2 see page 29, right-hand column, paragraph 1 - paragraph 2 see page 30, right-hand column, paragraph 2 - page 31, right-hand column, paragraph 1	1-6
Y	& MEETING OF THE ROYAL BELGIAN SOCIETY FOR ENT, HEAD AND NECK SURGERY, February 1995, BRUSSELS, -----	1-6